

# The Conceptual Structure of the Integrated Exposure Uptake Biokinetic Model for Lead in Children

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The integrated exposure uptake biokinetic model for lead in children was developed to provide plausible blood lead distributions corresponding to particular combinations of multimedia lead exposure. The model is based on a set of equations that convert lead exposure (expressed as micrograms per day) to blood lead concentration (expressed as micrograms per deciliter) by quantitatively mimicking the physiologic processes that determine blood lead concentration. The exposures from air, food, water, soil, and dust are modeled independently by several routes. Amounts of lead absorbed are modeled independently for air, food, water, and soil/dust, then combined as a single input to the blood plasma reservoir of the body. Lead in the blood plasma reservoir, which includes extracellular fluids, is mathematically allocated to all tissues of the body using age-specific biokinetic parameters. The model calculation provides the estimate for blood lead concentration for that age. This value is treated as the geometric mean of possible values for a single child, or the geometric mean of expected values for a population of children exposed to the same lead concentrations. The distribution of blood lead concentrations about this geometric mean is estimated using a geometric standard deviation, typically 1.6, derived from the analysis of well-conducted community blood studies. — *Environ Health Perspect* 106(Suppl 6):1513–1530 (1998). <http://ehpnet1.niehs.nih.gov/docs/1998/Suppl-6/1513-1530white/abstract.html>

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Assessments that recognize the multimedia nature of exposure to environmental toxicants are a significant improvement in assessing health risks. Assessments restricted to a single pathway of exposure can overlook situations in which integrated multimedia exposure pathways are collectively high enough to trigger health concerns. This is particularly true of lead exposure

because of the multisource, multiroute exposure to this toxicant.

This paper describes the development of an integrated model that applies data on environmental levels of lead to estimate impacts on children's blood lead levels. In developing this model, we focused on three emerging paradigms of in-depth environmental assessment:

- Assessment of the multipathway, multisource nature of environmental exposure.
- Application of pharmacokinetic information to assessments of internal dose or body burden.
- Assessment of variability in exposures and risks that result from differences in an individual's immediate environment, behavior, and physiology.

This paper describes the conceptual structure and scientific foundations of the integrated exposure uptake biokinetic (IEUBK) model for lead in children which has been developed over a 10-year period at the U.S. Environmental Protection Agency (U.S. EPA). An early version of this model was applied by the U.S. EPA in the evaluation of children's exposures resulting from atmospheric emissions from point sources of lead (1). In 1990 the U.S. EPA external Clean Air Science Advisory Committee examined and found acceptable the staff reports by the U.S. EPA Office of Air Quality Planning and Standards describing the model and these applications (2). Subsequently, the model was adapted and refined for use in assessing total lead exposures and application in the development of soil remediation goals at hazardous waste sites. A committee of the U.S. EPA Science Advisory Board reviewed these model applications in 1992 (3). The committee concluded that the model approach was sound and they recommended refinements to model specifications and input parameters. In response to this review, the U.S. EPA has further refined the IEUBK model and has published software, documentation, and guidance for the model (external peer review was also obtained for these materials). The available computer software and model documentation is detailed at the end of this paper. The reader should note that two other papers in this *EHP Supplement* provide further information regarding the IEUBK model. The paper by Hogan et al. (4) describes the validation process that has been followed with the IEUBK model and presents comparisons between model predictions and observations in epidemiologic studies. The paper by Zaragoza and Hogan (5) details the verification process that has been followed for the computer code for the IEUBK model.

This modeling effort focuses on young children as a population subgroup that is proportionately more highly exposed to

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Abbreviations used: ATSDR, Agency for Toxic Substances and Disease Registry; ECF, extracellular fluid; IEUBK model, integrated exposure uptake biokinetic model for lead in children; GI, gastrointestinal; GSD, geometric standard deviation; RfD, reference dose; U.S. EPA, U.S. Environmental Protection Agency; U.S. FDA, U.S. Food and Drug Administration.

environmental lead and significantly more sensitive to the toxicologic effects of these exposures than are adults.

In the United States and many other parts of the world, ongoing public health and regulatory measures have achieved major reductions in children's blood lead levels. In particular, the U.S. Environmental Protection Agency's (U.S. EPA) phasedown of leaded gasoline, the U.S. Food and Drug Administration's (U.S. FDA) actions to reduce dietary lead, and the Consumer Product Safety Commission's ban on lead in paint have sharply curtailed young children's typical lead exposures in the United States. Nonetheless, home- and neighborhood-specific sources of lead exposure remain a substantial public health concern. Similarly, in communities with extensive environmental contamination from past smelting, mining, and other metallurgical activities, substantial proportions of young children historically have had blood lead concentrations that exceeded the 10  $\mu\text{g}/\text{dl}$  level. To address these issues, the U.S. EPA, in cooperation with the Agency for Toxic Substances and Disease Registry (ATSDR) and the health and environmental agencies of several state governments, has initiated risk assessments of specific sites where children are believed to be at risk through exposure to lead.

The sources and pathways of childhood lead exposure are complex, involving contaminated soils and lead-based paints, with dust movement playing a major intermediary role as a pathway between sources of exposure. In some communities, lead in drinking water has been leached from brass plumbing fixtures and leaded solder (the latter now having been banned). Airborne exposures remain a concern for children living in the vicinity of certain point sources of emissions. Dietary lead, although substantially reduced, provides an additional source of lead intake to the population, as does the child's initial body burden, which is derived from the mother.

Blood lead concentration is the principal biologic indicator used to identify children who have elevated lead exposures; in particular, the Centers for Disease Control and Prevention (6), the U.S. EPA (7), and the ATSDR (8) have identified a blood lead concentration of 10  $\mu\text{g}/\text{dl}$  as a level of concern for health risks to children.

Assessing the impact of multimedia environmental sources in causing elevated blood lead levels is a difficult and sometimes contentious matter. This is particularly true since the environmental health

community has less historical experience in quantitatively addressing the soil and house dust exposure pathways that are now primary concerns. In resolving today's complex lead issues, researchers and health officials need to bring to bear the full range of available tools for understanding and assessing lead risks. These tools include prospective and case-control methods in epidemiology, isotopic ratio studies to identify sources of lead exposure, and mathematical modeling to address multipathway lead exposure and pharmacokinetics.

At the outset, we think it is important to address a generic question that is frequently raised: "Why use a model to estimate environmental lead risks when you can measure children's blood lead levels directly?" A first answer is that public health concerns dictate the prevention or minimization of exposure to lead, particularly for young children. When lead is measured in children's blood, exposure has already occurred. Furthermore, although thorough community blood lead studies can provide very useful data, they are not simple or inexpensive to conduct and interpret. Relatively large numbers of subjects are needed to obtain estimates of community risks, and reliable studies need to be based on community census or random sampling approaches that achieve high response rates. One concern is that children living in residential circumstances that are most likely to promote lead exposures may not be representatively captured in blood lead screening surveys with volunteer participants. Strong seasonal effects on blood lead levels (9) also complicate and delay the conduct and interpretation of blood lead surveys.

More fundamentally, modeling is generally recognized as advantageous in answering types of questions that are not easily addressed through blood lead monitoring. For example:

- What reductions in risks of elevated blood lead levels can be achieved when certain control actions are taken?
- What are the likely future risks at residences or properties where children are not currently present or at properties where housing development is anticipated?
- At what levels of environmental lead concentrations will children have risks of elevated blood lead levels in excess of goals for health protection?

It should, however, be emphasized that mathematical models should not be used as a substitute for blood lead measurement

and medical assessment for a specific child at risk. Medical evaluation can take into account specific information on behavior and risk factors, such as nutritional status, that are beyond the scope of a broadly applicable environmental risk model.

## Overview of the IEUBK Model

The focus of the integrated exposure uptake biokinetic (IEUBK) model for lead in children is the prediction of blood lead concentrations in young children exposed to lead from several sources and by several routes. The model is a four-step process that mathematically and statistically links environmental lead exposure to blood lead concentrations for a population of children (0–84 months of age). Figure 1 provides a schematic showing the sources of exposure to environmental lead and the absorption and processing of lead by the human body (10).

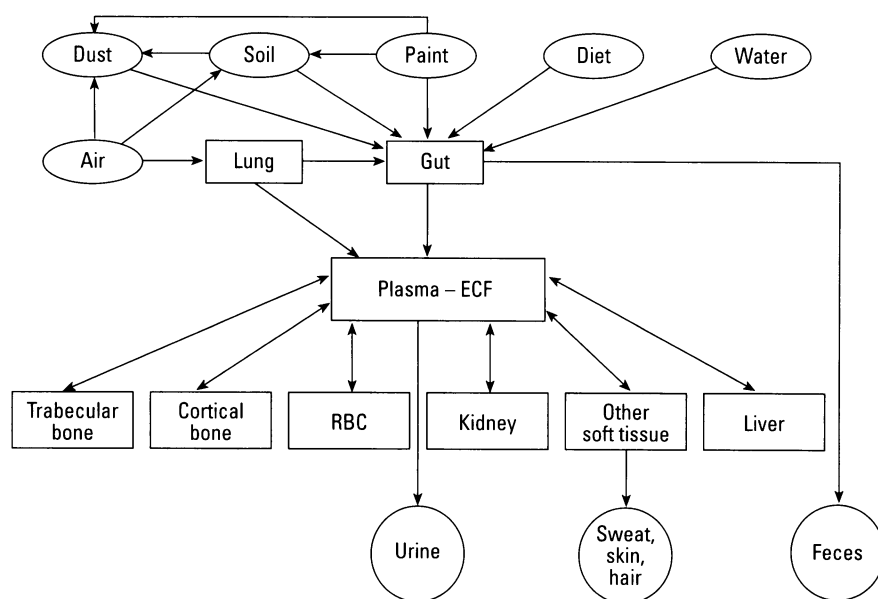
The four model components each reflect a different aspect of the overall biologic process:

### Exposure

Exposure can be thought of as the contact of a chemical, or other agent, with the absorption or exchange boundaries of an organism, such as the gut, lungs, and skin. Quantitation of a child's exposure to lead ( $\mu\text{g}/\text{day}$ ) requires estimation of the concentration of lead in the environmental media that the child contacts (usually  $\mu\text{g}/\text{g}$ ,  $\mu\text{g}/\text{m}^3$ , or  $\mu\text{g}/\text{l}$ ), multiplied by a term to describe the amount of contact the child has with the medium (usually  $\text{g}/\text{day}$ ,  $\text{m}^3/\text{day}$ , or  $\text{l}/\text{day}$ ), and a term for the duration of that contact (usually days). The results from the exposure component of the IEUBK model are estimated intake rates for the quantities of lead inhaled or ingested from environmental media. The media addressed by the IEUBK model include soil, house dust, drinking water, air, and food. Paint is usually addressed in terms of its contribution to the measured concentrations of lead in soil or house dust.

### Uptake

The uptake component models the process by which lead intake (lead that has entered the child's body through ingestion or inhalation) is transferred to the blood plasma. Uptake ( $\mu\text{g}/\text{day}$ ) is the quantity of lead absorbed per unit time from portals of entry (gut, lung) into the systemic circulation of blood. Only a fraction of the lead entering the body through the respiratory or gastrointestinal (GI) tracts is actually



**Figure 1.** Conceptual diagram of the movement of environmental lead into and through the human body. The oval shapes show environmental media and the pathways of uptake. The rectangular boxes show the biokinetic compartments of the IEUBK model. The large rectangle is the blood plasma compartment central to the distribution of lead in the body. The circular boxes represent the elimination pathways. Data from the U.S. EPA (10).

absorbed into the systemic circulation. This absorption fraction is, by convention, termed bioavailability and provides the most convenient parameterization of the uptake process. The IEUBK model addresses the different bioavailabilities of lead from different environmental media and provides for a partial saturation of absorption at high levels of lead intake.

### Biokinetics

The biokinetic component of the IEUBK model is a mathematic expression of the movement of absorbed lead throughout the body over time by physiologic or biochemical processes. The biokinetic component converts the total lead uptake rate from the uptake component into an input to the central plasma-extracellular fluid (ECF) compartment. Transfer coefficients are used to model movement of lead between the internal compartments and to the excretion pathways. These quantities are combined with the total lead uptake rate to continuously recalculate the lead masses in each of the body compartments and especially the changing concentration of lead in blood.

### Variability

An important goal of the IEUBK model is to address variability in blood lead concentrations among exposed children. Children having contact with the same concentrations

of environmental lead can develop very different blood lead concentrations due to differences in behavior, household characteristics, and individual patterns of lead uptake and biokinetics. The IEUBK model uses a log-normal probability distribution to characterize this variability. The biokinetic component output provides a central estimate of blood lead concentration, which is used to provide the geometric mean parameter for the log-normal model. The interindividual variability in blood lead concentrations is characterized by a geometric standard deviation (GSD). The recommended default value for this parameter (1.6) was derived from empirical studies with young children where both blood and environmental lead concentrations were measured.

### The IEUBK Model Exposure Component

Lead is a naturally occurring nonnutrient metal and normally follows environmental pathways similar to those of nutrients such as calcium. Lead has a multitude of sources in the environment and thus has many pathways from environmental sources into the child's body (11). The most important contact points for exposure to the child are the GI tract and the lungs.

The IEUBK model is structured to integrate the multiple pathways of exposure in the child's environment in estimating the

blood lead levels in children in realistic environmental settings (Figure 1). Almost all media in the child's environment can act as sources of lead intake for the child. Lead in food, drinking water, soil, dust, air, paint, and other sources (e.g., medicinals) enters the child's body through the GI tract. Lead in the air enters the body through both the lungs and particulate transport to the GI tract.

Assessment of the risk to a child from exposure to lead is dependent on the careful and thorough characterization of lead in the child's environment. This exposure unit is usually considered to be restricted to the media in the child's home and yard, although the inclusion of alternate or additional sources of exposure, such as those at a daycare center or alternate care-giver's home, can be part of the total exposure scenario developed in the model.

The IEUBK model identifies the environmental parameters for which inputs must be provided by the user in order to characterize the typical child's exposure. All media-specific contact rates and media-specific lead concentrations used to derive the media-specific lead intake rates are accessible to the user of the computer model. In lieu of user input, default values for these parameters initialize the model. These default values are central values derived from *a*) empirical data in the open literature that include values for the lead concentrations commonly found in the various media and diet, *b*) rates at which these media can be expected to enter the child's body (such as the soil/dust ingestion rate), and *c*) reasonable estimates of exposure durations. Exposure parameters can be changed for each year of exposure. It is the responsibility of the user to ensure that the default values or other parameter values are appropriate for the specific application of the model. The exposure parameters in the model are defined in Table 1; default values are given in Table 2.

### Importance of Exposure to Dust and Soil

Dust lead is found in both the indoor and outdoor environments of the child. The mouthing habits of a small child provide an easy route for intake of lead into the body. Outside, the child comes into contact with soil dust by contact with play surfaces.

The ability of soil dust to move easily through the environment by sticking to hands, shoes, toys, pets, and other objects and its easy movement by atmospheric transport facilitate its movement into the

**Table 1.** Variables and parameters used in exposure component of the IEUBK model.

Variable or parameter name	Definition
$C_{air, indoor}$	Concentration of lead in indoor air, $\mu\text{g}/\text{m}^3$
$C_{air, outdoor}$	Concentration of lead in outdoor air, $\mu\text{g}/\text{m}^3$
$C_{air, TWA}$	Concentration of lead in air, time-weighted average, $\mu\text{g}/\text{m}^3$
$C_{dust, daycare}$	Concentration of lead in dust at daycare, $\mu\text{g}/\text{g}$
$C_{dust, indoor sources}$	Concentration increment of lead in dust due to paint and other indoor sources, $\mu\text{g}/\text{g}$
$C_{dust, resid}$	Concentration of lead in dust at primary residence, $\mu\text{g}/\text{g}$
$C_{dust, resid2}$	Concentration of lead in dust at second residence, $\mu\text{g}/\text{g}$
$C_{dust, school}$	Concentration of lead in dust at school, $\mu\text{g}/\text{g}$
$C_{soil}$	Concentration of lead in outdoor soil, $\mu\text{g}/\text{g}$
$C_{water}$	Concentration of lead in drinking water, $\mu\text{g}/\text{g}$
$IN_{air}$	Intake rate of lead from air into lungs, $\mu\text{g}/\text{day}$
$IN_{diet}$	Intake rate of lead from diet, $\mu\text{g}/\text{day}$
$IN_{dust}$	Intake rate of lead from ingested dust, $\mu\text{g}/\text{day}$
$IN_{soil, outdoor}$	Intake rate of lead from soil ingested outdoors, $\mu\text{g}/\text{day}$
$IN_{water}$	Intake rate of lead from drinking water, $\mu\text{g}/\text{day}$
$IR_{dust}$	Ingestion rate, dust, $\text{g}/\text{day}$
$IR_{dust, daycare}$	Ingestion rate, dust from daycare, $\text{g}/\text{day}$
$IR_{dust, resid}$	Ingestion rate, dust from primary residence, $\text{g}/\text{day}$
$IR_{dust, resid2}$	Ingestion rate, dust from second residence, $\text{g}/\text{day}$
$IR_{dust, school}$	Ingestion rate, dust from school, $\text{g}/\text{day}$
$IR_{soil, outdoor}$	Ingestion rate, soil outdoors, $\text{g}/\text{day}$
$IR_{soil + dust}$	Ingestion rate, total mass of soil and dust, $\text{g}/\text{day}$
$IR_{water}$	Ingestion rate, water, $\text{liter}/\text{day}$
$k_{air, dust}$	Ratio of increment in indoor dust concentration to outdoor air concentration, $\mu\text{g}/\text{g}/\mu\text{g}/\text{m}^3$
$k_{air, in/out}$	Ratio of concentration of indoor air to outdoor air, unitless
$k_{soil, dust}$	Mass fraction of soil-derived dust in house dust, unitless
$t_{indoor}$	Time spent indoors, $\text{hr}/\text{day}$
$t_{outdoors}$	Time spent outdoors, $\text{hr}/\text{day}$
$VR$	Ventilation (inhalation rate), $\text{m}^3/\text{day}$
$WF_{soil}$	Fraction of total soil and dust intake that occurs as soil intake, unitless

child's indoor environment. Lead in indoor dust is constantly available as an exposure source for the child.

Soil ingestion studies are based on mass balance methodologies that measure the fecal excretion of trace elements found in soils. In these studies the quantity of tracer due to dietary ingestion is subtracted from the quantity excreted and the remaining balance is attributed to the ingestion of soil. Note that soil ingestion measurements do not account for additional quantities of dust and soil contamination that may be derived through the storage and preparation of foods. The duplicate diet samples collected to represent dietary intake of tracers will implicitly contain dust and soil present due to the storage and preparation of foods. This quantity of intake is attributed to diet and has been subtracted out in published estimates of soil ingestion.

The IEUBK model separately estimates lead intake from the ingestion of outdoor soil (interpreted as primarily surface soil dust) and indoor dust. For each of these media, lead intake by the child is modeled using age-specific media ingestion rates

( $IR_{media}$ ) and concentrations ( $C_{media}$ ). Ingestion rates for dust and soil are calculated as fractions of a total ingestion rate:

$$IR_{dust} = (1 - WF_{soil}) \times IR_{soil + dust} \quad [1]$$

$$IR_{soil, outdoor} = WF_{soil} \times IR_{soil + dust} \quad [2]$$

The ingestion rate for soil and dust ( $IR_{soil + dust}$ ) incorporates the ingestion of both outdoor soil and indoor dust. Soil ingestion measurements in tracer studies implicitly account for the fact that some soil is ingested indoors as a component of house dust. Note, however, that house dust contains materials other than soil; thus, the total quantity of soil and dust ingested will tend to exceed the quantity of soil ingested.

Lead intake from soil is given by the product of soil concentration and the age specific rates for soil ingestion:

$$IN_{soil, outdoor} = C_{soil} \times IR_{soil, outdoor} \quad [3]$$

The concentration term should represent a central estimate of the lead concentration in soils that a child is likely to ingest. In general, the arithmetic mean concentration for a residential yard or specific play areas provides an appropriate concentration term for risk assessment. The use of the arithmetic mean is predicated on the presumption that, in the absence of detailed child-specific data, a reasonable central assumption is that a child will have equal contact with soils throughout a residential lot. This soil contact is assumed to occur on a routine, repeated basis. In the assessment of a residential environment, site-specific measurement data on soil concentrations in a child's yard or other exposure unit are necessary.

Methodologically, the ingestion of interior house dust is assessed similarly to the ingestion of outdoor soil. Measurement data on household dust lead concentrations are applied for assessment of existing residential risks. The measured dust concentration will reflect the contributions of soil, paint, and air deposition to indoor dust lead.

$$IN_{dust} = C_{dust, resid} \times IR_{dust, resid} \quad [4]$$

Where appropriate the concentration of lead in indoor dust may be modeled as a sum of dust derived from soils, dust derived from deposition of airborne lead, and dust contributed by other sources:

$$C_{dust, resid} = k_{soil, dust} \times C_{soil} + k_{air, dust} \times C_{air, outdoor} + C_{dust, indoor sources} \quad [5]$$

Constants of proportionality are applied to estimate the contributions of outdoor soil and airborne lead to indoor dust. In particular,  $k_{soil, dust}$ , represents the mass fraction of soil-derived dust in house dust. This calculation requires the assumption that the measured concentrations of lead in outdoor soil are sufficiently representative of the concentrations in soil materials that are transported indoors.

Where children are exposed to dust at more than one location (e.g., home and day care), dust ingestion can be proportioned among the locations. In cases where children would engage in similar activities at different locations, the dust intake can be proportioned according to the fraction of a child's indoor, waking hours spent in the locations. Where there are multiple locations of exposure, a child's intake of lead from dust is expressed as

**Table 2.** IEUBK default values for exposure parameters.

Parameter	Default value	Units
Outdoor air lead concentration	0.10	µg/m
Ratio of indoor to outdoor air lead concentration	0.30	unitless
Time outdoors		
Age		
0–1 year (0–11 months)	1	hr/day
1–2 years (12–23 months)	2	
2–3 years (24–35 months)	3	
3–7 years (36–83 months)	4	
Ventilation rate		
Age		
0–1 year (0–11 months)	2	m <sup>3</sup> /day
1–2 year (12–23 months)	3	
2–3 years (24–35 months)	5	
3–4 years (36–47 months)	5	
4–5 years (48–59 months)	5	
5–6 years (60–71 months)	7	
6–7 years (72–84 months)	7	
Dietary lead intake		
Age		
0–1 year (0–11 months)	5.53	µg/day
1–2 year (12–23 months)	5.78	
2–3 years (24–35 months)	6.49	
3–4 years (36–47 months)	6.24	
4–5 years (48–59 months)	6.01	
5–6 years (60–71 months)	6.34	
6–7 years (72–84 months)	7.00	
Lead concentration in drinking water	4	µg/liter
Drinking water ingestion rate		
Age		
0–1 year (0–11 months)	0.20	liters/day
1–2 year (12–23 months)	0.50	
2–3 years (24–35 months)	0.52	
3–4 years (36–47 months)	0.53	
4–5 years (48–59 months)	0.55	
5–6 years (60–71 months)	0.58	
6–7 years (72–84 months)	0.59	
Concentration for alternate sources of drinking water		
First-draw water	4	µg/liter
Flushed water	1	
Fountain water	10	
Fraction of water intake from alternate sources		
First-draw water	0.50	unitless
Flushed water	0.35	
Fountain water	0.15	
Lead concentration in soil and dust		
Soil	200	µg/g
Dust	200	
Soil ingestion as a fraction of total soil and dust ingestion	0.45	unitless
Mass fraction of soil-derived dust in house dust	0.70	unitless
Ratio of increment in dust lead concentration to outdoor air lead concentration	100	µg/g per µg/m <sup>3</sup>

$$\begin{aligned}
 IN_{dust} = & C_{dust, resid} \times IR_{dust, resid} \\
 & + C_{dust, school} \times IR_{dust, school} \\
 & + C_{dust, daycare} \times IR_{dust, daycare} \\
 & + C_{dust, resid2} \times IR_{dust, resid2}
 \end{aligned} \quad [6]$$

The IEUBK model does not contain an explicit component for lead-based paint ingestion. Since old lead-based paint can contain in excess of 35% lead, ingestion of even small quantities of paint chips can cause serious lead intoxication. As discussed below, the IEUBK model was not developed to address such acute exposures. If there are data to support estimates of children's average daily intake of paint

materials, that intake can be included using the alternate source option in the soil/dust menu in the computer model. As noted above, model assessments done using measurement data for house dust implicitly include the contribution of lead-based paint to the dust lead concentration.

### Other Sources of Lead Exposure

Dietary lead exposure is determined by one of two methods: *a*) direct specification, or *b*) the alternative diet model. Dietary lead exposure is the product of the amount of food consumed in each category and the concentration of lead in the food item. Under the direct specification of food

categories, the dietary intake is set to a user-specified, age-dependent lead intake for diet. The default values in the model are constructed from data from the U.S. FDA Market Basket Survey data for lead concentrations from 1988 (1), and from the Pennington study of food consumption (12), which reflect the mean dietary intake based on the child's age. Because of reductions or elimination of major sources of lead in food (lead-soldered cans and air deposition on food crops), the market basket route of dietary lead exposure is believed not to have changed markedly since about 1990, especially for children under seven years of age. If the model is used with historical exposures (during the years 1982–1989), the dietary intake data can be adjusted to the year when the data were collected. The dietary intake estimates may be updated as further data become available. There are no reliable data in the market basket format for dietary lead prior to 1982.

Under the alternative diet model, child-specific estimates can be included using data on local sources of garden produce, fish, or game meat. The user specifies the lead concentration for the alternate sources by category (fruit, vegetables, fish, game animals) and designates the percentage of the comparable market basket category to be replaced by the alternate source.

The air exposure model considers both indoor and outdoor air lead exposure in determining the child's overall lead exposure, in which, as a default, the indoor air lead concentration is calculated as a percentage of the outdoor air concentration. A time-weighted average air lead concentration is calculated from the indoor and outdoor air lead concentrations, where the user can specify the number of hours per day that a child spends outdoors for each age range. Finally, the air exposure is calculated as the product of the time-weighted air lead concentration and a user-specified, age-dependent ventilation (inhalation) rate.

$$C_{air, indoor} = k_{air, in/out} \times C_{air, outdoor} \quad [7]$$

$$\begin{aligned}
 C_{air, TWA} = & \\
 & \frac{t_{outdoor} \times C_{air, outdoor} + t_{indoor} \times C_{air, indoor}}{24 \text{ hr}}
 \end{aligned} \quad [8]$$

$$IN_{air} = C_{air, TWA} \times VR \quad [9]$$

The default outdoor air lead concentration is  $0.1 \mu\text{g}/\text{m}^3$ , which approximates the average urban air lead concentration in the United States following the phasedown of lead in gasoline (13). For the ventilation rate, the lead model uses midrange values from the age-specific ranges of child ventilation rates established by the U.S. EPA (1).

In monitoring studies, water lead concentrations may be derived from first-draw standing samples, partially flushed samples, or fully flushed samples, all of which may differ significantly in lead concentration. In the model, water lead exposure is determined by one of two methods: *a*) direct specification of the lead concentration, where the water intake is calculated as the product of a user-specified, age-dependent water consumption rate and a user-specified water lead concentration, or *b*) an alternative format, where the user specifies the amount and lead concentration of water consumed as first draw versus flushed. The user may also specify the amounts and concentration consumed from water fountains. For the direct calculation:

$$IN_{\text{water}} = C_{\text{water}} \times IR_{\text{water}} \quad [10]$$

As shown in Table 1, consumption rates for drinking water ingestion rates for most of the modeled age groups are approximately 0.5 liters/day (10). If no household-specific or relevant community water lead data are available, a default value of  $4 \mu\text{g}/\text{liter}$  is used in the model, based on analyses of water consumption data (14).

Under the alternative water model, the water intake is calculated as a product of the same user-specified, age-dependent water consumption rate and a constant water lead concentration that is calculated as a weighted average of user-specified, constant water lead concentrations from the first-draw sample on a home faucet, a sample from a flushed home faucet, and a water fountain outside the home. The concentrations are weighted by user-specified constant fractions of consumed water of each type (15). Default values for these parameters are shown in Table 2.

Other consumer products may have a nontrivial potential for exposure; these exposures are considered under the other sources menu in the IEUBK computer model. They include the use of lead-glazed or soldered cooking and food preparation utensils, ethnic or regional preferences for food products and cosmetics with high lead content, and the use of oral ethnic medicines, such as *empacho* or *azarcon*

that have high concentrations of lead and are known to have caused cases of acute lead poisoning in children (16,17). No general recommendations about parameter values for these sources of lead can be made to assist in the modeling of such exposures. Approximate intakes for oral medicines may be estimated from recommended or customary doses for children.

### Maternal Contribution

The model algorithm assumes that the infant's blood lead level at birth is a fraction of the maternal blood lead levels. The amounts of lead in the blood and other tissues in the newborn infant are calculated to be consistent with concentration ratios observed in autopsies of newborn infants (18). The maternal transfer of lead to the child while *in utero* provides the child's initial exposure to lead. This transfer is defined in the model. The lead that is stored in the tissues of the newborn child is calculated as 85% of the maternal blood lead level at birth; the default maternal blood lead concentration in the model is  $2.5 \mu\text{g}/\text{dl}$ .

### The IEUBK Model Uptake Component

The IEUBK uptake component models the process in which lead intake is transferred to the blood plasma. Uptake is the rate at which lead from all media is taken into the blood; that is, the quantity of lead absorbed per unit time from portals of entry (gut, lung) into the systemic circulation of blood. The absorption fraction for lead intake, termed the bioavailability, is portal-of-entry and medium specific. That is, the absorption of lead from the respiratory tract is assessed independently from that of the GI tract. Additionally, within a particular portal-of-entry (e.g., GI tract), bioavailability is a function of the medium (e.g., water, food, dust) in which the lead is delivered.

### Mechanisms of Absorption

In the United States today, the predominant route of exposure of children to environmental sources of lead is through the GI tract. Lead absorption in the GI tract is believed to proceed by several cellular mechanisms involving the enterocytes (cells lining the intestinal wall) (19,20). Absorption also entails complex interactions of lead with the uptake of essential nutrients such as calcium, iron, and phosphate (21,22).

The first uptake mechanism is postulated to be diffusion through the gut lumen, driven by a concentration gradient from the luminal surface lining the intestine to the

basolateral surface. This mechanism is likely to depend to some extent on the concentration of unbound lead ions ( $\text{Pb}^{2+}$ ), and consequently would be influenced by the solubility characteristics of lead species of interest. This process may be characterized as passive diffusion, requiring no energy input. It involves either intracellular or paracellular movement of lead across the wall. Paracellular transport would entail movement across the area between cells called tight junctions (19,20).

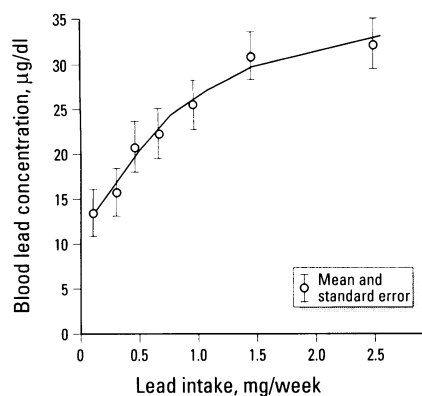
Lead may also enter the gut tissue (but not necessarily the bloodstream) by pinocytosis or other vesicular mechanisms. In pinocytosis, lead-bearing media in the liquid microregion of the gut are engulfed by the (enterocyte) cell membrane. Such encapsulation may involve lead in either a truly soluble or an emulsified/suspended form that is then carried to blood or target sites. This process is biochemically analogous to handling of solid particles in phagocytosis (19,20).

Another important transport mechanism is energy-driven facilitated transport, exploiting biologically significant homeostatic mechanisms for calcium and iron transport (e.g., calcium-binding protein [CaBP] or Calbindin D), and under the control of an enzyme (Ca,Mg-dependent ATPase) involved in the absorption and regulation of blood calcium levels and located in the basolateral membrane of mucosal epithelial cells. This active component of lead absorption displays a strong age dependence, being more important at younger ages.

### Modeling Lead Uptake

Although the results of experimental studies can be described quantitatively, the biologic and biochemical mechanisms in lead bioavailability are not yet completely understood. There is, however, a useful characterization of lead absorption mechanisms as either saturable (facilitated) or nonsaturable (passive). These various and complex biochemical and cellular mechanisms obviously have important implications for experimental models of lead bioavailability in humans, particularly with reference to comparison of *in vivo* to *in vitro* simple chemical simulation models.

Human data suggest a curvilinear relationship between lead intake and lead absorption. In duplicate diet studies of bottle-fed infants (5–7 kg bw) exposed to lead in water and in formula mixed with contaminated water, Sherlock and Quinn (23) were able to quantify the nonlinear



**Figure 2.** Dose-dependent relationship between dietary lead (formula mixed with water) and blood lead in infants. Data from Sherlock and Quinn (23).

dose dependence of children's blood lead concentrations on lead intake (Figure 2). Studies in nonhuman primates also suggest a nonlinear relationship between lead intake and blood lead levels (24). Similar dose dependency has been demonstrated in other animal models (25,26). This dose dependence is consistent with an active transport mechanism that requires lead-inhibited enzyme(s) for its operation and that also becomes saturated at higher lead doses (27,28). The physiologic mechanisms that account for these observations of curvilinearity are not completely established. We have interpreted this nonlinear relationship as indicating lead absorption by at least two mechanisms (facilitated and passive). In the IEUBK model, total lead uptake from the gut is treated as the sum of saturable (facilitated) and nonsaturable (passive) components.

Experimental studies of soil lead absorption using appropriate animal models and feeding patterns analogous to those of human children are being carried out by the U.S. EPA. Preliminary results (29) are consistent with the assumptions used in the model but require more complete analyses. The current parameters of the model are based on statistical analyses of some experimentally measurable quantities in these studies and in older studies in human children (23).

In extending these results to a mixed multimedia gut intake scenario, the model assumes that linear absorption at low intake rates is an appropriate characterization for the available lead. When doses are relatively low, human or appropriate experimental animal data may be applied to estimate the fractional absorption of lead. A fractional absorption estimate implicitly combines

elements affecting the dissolution of solid particles (particle size, chemical speciation, matrix embedding, and stomach pH at different times after meals) and other aspects of absorption for which we have no comprehensive quantitative model at this time. Although the characterization of gut uptake by a fractional absorption value is conceptually straightforward, it does not characterize the full complexity of the absorption processes. Absorption occurs in different segments of the gut, and lead concentrations in these segments depends on acidity, binding of lead to total gut contents, including minerals and fibers, and other factors. It is not likely that knowledge of all of these factors would be available in any real-world childhood lead exposure scenario.

There is a developmental or age dependency for the extent of lead absorption in both humans and experimental animals (11,19). Young children absorb more lead than do adults (30). Experimental animal studies support the human data. Studies using rats showed that preweanling animals absorb 40 to 50 times more of a given dose of lead than adult animals (31–33), and infant monkeys absorb 16 to 21 times more lead than adult monkeys (34). Possible mechanisms for this age dependence have been discussed (19,35). The design or interpretation of bioavailability studies, aimed at assessing lead absorption for children, must consider age dependence of uptake of lead in any adjustment of the bioavailability parameter in the model.

### Respiratory Tract

Lead on aerosol particles must be inhaled and deposited before pulmonary absorption can occur. Particles inhaled but not deposited may be exhaled or trapped by the mucociliary lift mechanism and ingested. The number of inhaled particles of a given size range varies with the ambient particle density and size distribution and the breathing rate. The breathing rate varies with age and physical activity. Inorganic lead in ambient air consists primarily of particulate aerosols with a size distribution determined largely by the nature of the source and proximity to this source. In rural and urban environments, this size distribution is usually from 0.05 to 1  $\mu$ . Near point sources, particles greater than 10  $\mu$  can prevail.

Particles greater than 2.5  $\mu$  in diameter are deposited in the ciliated regions of the nasopharyngeal and tracheobronchial airways, where they are passed to the GI tract

by the mucociliary lift mechanism. Particles small enough to penetrate the alveolar region can be dissolved and absorbed into systemic circulation or ingested by macrophagic cells. Evidence that lead does not accumulate in the lungs suggests that lead entering the alveolar region is completely absorbed (36,37). Rabinowitz et al. (38) found about 90% of the deposited lead was absorbed daily. In the model, the default assumption is that 35% of inhaled lead reaches the absorbing surface, and 100% of this is absorbed.

### Percutaneous Absorption

Certain organo-lead compounds (e.g., lead acetate) have a limited ability to penetrate the skin. However the predominant forms of inorganic lead in the environment are believed to exhibit poor dermal penetrability (39); consequently, the IEUBK model does not address exposure/uptake via the dermal route of exposure.

### Medium-Specific Model Parameters for Bioavailability

**Soil and Dust.** The current assumption in the IEUBK model is that 30% of dust and soil lead intake is absorbed into the blood. Some investigators (40) argue that the bioavailability of lead in soil from some old mining sites is much less than that of dissolved lead salts for several reasons: *a*) large lead particles may not be completely dissolved in the GI tract; *b*) the solubility of chemical species commonly found in mine wastes, particularly lead sulfide, is much lower than that of other lead salts. These hypotheses are based on studies with small laboratory animals such as rats (41,42), and although the results may be qualitatively relevant to humans, it is not clear how they should be extrapolated to humans or to other large animals such as baboons or swine with physiologic digestive properties quite different from rodents.

**Diet.** The absorption of lead from food and liquid diet by infants up to 6 months old is known to be very high (43); it is much lower in adults (44–47). Less is known about changes in lead absorption from diet for older infants, toddlers, and children. A value of 50% was selected as an intermediate level in children and infants (48).

The exact form of the dietary lead absorption coefficient in humans is not known. There is evidence that the absorption of lead in food by infants is quite high—at least 40 to 50%. The range cited by the U.S. EPA is 42 to 53% (48).

Although absorption probably decreases after infancy, we have no direct evidence on how to interpolate this range for children 2 to 6 years of age. A smoothing of the absorption data from infant to juvenile baboons in the studies by Harley and Kneip (49) has been proposed as a basis for extrapolation by the U.S. EPA (1). In view of the uncertainty about this, the IEUBK model uses the same default value of 50% for ages 1 to 6 years. This value will, at worst, slightly overestimate dietary lead uptake in older children.

**Water.** The bioavailability of dissolved lead salts in drinking water is very high when consumed by adults between meals (44), and very low when consumed with meals. The maximum retention of lead in children probably exceeds that of adults, which is about 60% on an empty stomach, and absorption is likely to be only somewhat greater than retention. Considering that some water intake likely occurs concurrently with meals, a value of 50% is recommended as plausible.

**Lung Absorption.** The range of values for child lung absorption was established by the U.S. EPA (1) as 25 to 45% for young children living in nonpoint source areas, and 42% for those living near point sources. The default value used in the IEUBK model is 32%. Changes in the source of airborne particulates may also affect lung absorption.

## Model Calculation of Active and Passive Absorption

Individual intake rates from six sources (air, food, drinking water, soil, dust, and other) are calculated in the exposure component

of the IEUBK model. Lead uptake is modeled in a calculation with two main steps. First, the amount of lead that would be absorbed in the absence of saturation effects is determined ( $UP_{poten}$ ). Then, through partitioning of absorption between the active and passive pathways, the net absorption is estimated.

The total lead that is available for absorption ( $UP_{poten}$ ) is equal to the sum of the products of ingested lead ( $IN_{media}$ ) multiplied by the absorption coefficients ( $ABS_{media}$ ) for each of the five ingestion categories and one inhalation category.

$$UP_{poten} = (ABS_{diet} \times IN_{diet}) + (ABS_{dust} \times IN_{dust}) + (ABS_{water} \times IN_{water}) + (ABS_{soil} \times IN_{soil}) + (ABS_{other} \times IN_{other}) + (ABS_{air} \times IN_{air}) \quad [11]$$

The recommended default values for the  $ABS_{media}$  parameters were described in the preceding section.

From this pool of lead, some is absorbed by passive uptake, some by active uptake. The passive uptake is considered nonsaturable and the active is saturable (Figure 3). The passive absorption fraction (PAF) is the proportionality parameter specifying the fraction of the total net absorption at low intake rates that is attributable to nonsaturable processes. Lead uptake by the passive pathway is assumed to be linearly proportional to intake at all dose levels.

$$UP_{passive} = PAF \times UP_{poten} \quad [12]$$

It is assumed that the fraction of absorbed lead intake that is absorbed by nonsaturable

processes (PAF) is the same for all media. The model default value for PAF is 0.20.

At low exposure, the quantity of lead absorbed by the active, saturable pathway is linear with intake:

$$UP_{active} = (1 - PAF) \times UP_{poten} \quad [13 - \text{low dose only}]$$

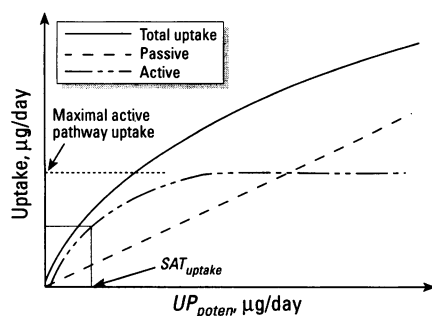
However, at higher doses, only a certain fraction of this amount will be absorbed. The equation for a rectangular hyperbola (the functional form applied with Michaelis-Menton enzyme kinetics) is used to represent saturable pathway absorption. The key parameter in this relationship is  $SAT_{uptake}$ , which represents the level of potential uptake ( $UP_{poten}$ ) at which the saturable pathway uptake reaches half of its maximum value. This half-saturation parameter depends on the age of the children. The model input parameter for  $SAT_{uptake}$  is its value at age 24 months (model default 100  $\mu\text{g}/\text{day}$ ). For other ages the value of  $SAT_{uptake}$  is obtained by scaling.

The amount of lead that is absorbed by saturable processes is calculated as:

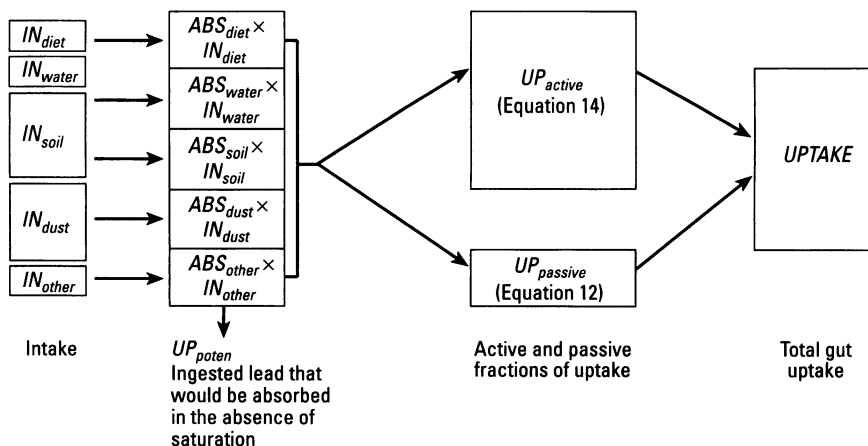
$$UP_{active} = \frac{(1 - PAF) \times UP_{poten}}{1 + UP_{poten} / SAT_{uptake}} \quad [14]$$

Total lead uptake is given by the sum of the active and passive components of uptake. Media-specific uptake rates are calculated proportionally to total intake.

Figure 3 illustrates the functional relationships between the saturable and nonsaturable pathways that are shown schematically in Figure 4. The uptake



**Figure 3.** Graphic illustration of the mathematical treatment of lead absorption in the IEUBK model showing the active and passive components.  $UP_{poten}$  represents the amount of intake that would be absorbed in the absence of saturation effects. Data from the U.S. EPA (15).



**Figure 4.** Conceptual model of gastrointestinal lead absorption. Data from the U.S. EPA (15).



model parameters are accessible to users of the IEUBK computer model.

### The IEUBK Model Biokinetic Component

The biokinetic component models the distribution of absorbed lead between blood and other body tissues, and the elimination of lead from the body via urine, feces, skin, hair, and nails. Underlying the biokinetic component of the IEUBK model is a compartmental structure that assumes that all of the lead in the body can be attributed to one of seven kinetically homogeneous compartments and that transfer between these compartments occurs through normal physiologic processes. As was shown in the schematic diagram in Figure 1, the compartmental structure of the model includes a central blood plasma-ECF compartment, a red blood cell (RBC) compartment, five peripheral body compartments, and three elimination pools.

The central compartment in the model is the plasma-ECF compartment. Several authors have demonstrated that except for intervals shorter than a few minutes, the ECF pool is kinetically indistinguishable from plasma (24,46,49,50). The total blood volume of distribution (including extracellular fluids), which has been estimated in adult men using stable lead isotope studies, is about 1.7 times the blood volume (51).

Separate body compartments are used in the model for red blood cells, trabecular bone, cortical bone, kidney, liver, and other soft tissues. These compartments were chosen for several reasons: the importance of some tissues, such as liver or kidney, as target sites of toxicity; the large potential lead burden of bone tissues; the conventional definition of certain compartments in many pharmacokinetic models; the availability of data describing the concentrations of lead found in these tissues; and the need for a system that would require little additional expansion for future applications.

Several models that describe the complicated kinetics of lead in bone have been developed (52–55). The IEUBK model uses separate trabecular and cortical bone compartments with similar parameters for young children in anticipation of future expansion of the model to older children or adults with differences in cortical and trabecular bone kinetics. Cortical and trabecular bones can accumulate large quantities of lead—at least 60% of the total body burden in children [U.S. EPA

reanalysis of data from (18,36,55–58)] and over 90% of body burden in adults with long exposure histories (1,11,55,56,59). Kidney and liver are included as separate compartments, with the remainder of the body compartments that have not been specifically defined in the model lumped together as “other soft tissues.”

Three elimination pathways are included in the model: pathways from the central plasma-ECF compartment to the urinary pool, from the compartment for other soft tissues to skin, hair, and nails, and from the liver to the feces. The biologic basis for this latter pathway is the excretion of bile by the liver into the GI tract, where it is subject to the digestive absorption processes of the uptake component.

The IEUBK model estimates transfer coefficients primarily from human data on tissue concentrations rather than the physiologically based pharmacokinetic approach using blood flow rates to organs and partition or diffusion coefficients across membranes or into bone tissue. The IEUBK computer model uses corresponding equations with discrete time steps in its computations. These equations represent lead masses, transfer rates, and elimination rates at the beginning and end of a time interval. The model solves the equations for compartment lead masses at the end of iteration time  $t$  in terms of compartmental lead masses at the beginning of the interval, and then determines the child's blood lead concentration at time  $t$ .

### IEUBK Model Biokinetic Parameter Estimates

**Available Data.** In developing estimates of parameter values, primary emphasis was placed on applying information from clinical studies of human children, including autopsy samples in young children who died from causes not related to lead exposure (18,36,57,58), and lead feeding and mass balance studies in human infants (23,43,55,60). When such data were not available, data from clinical studies of human adults were extrapolated with appropriate allometric scaling. Tissue concentration and kinetic data from primate studies were also evaluated in defining plausible parameter ranges for human children, but were not used as the primary basis for any biokinetic parameters. The derivation of parameters and equations that are used in the model has been detailed extensively in the IEUBK model technical documentation (15).

**Estimates of Specific Parameter Values.** To develop specific parameter values, the following steps were used:

- Tissue/blood lead concentration ratios were established. These concentrations were based primarily on autopsy samples from children, which were reported by Barry (18). Near steady-state conditions were assumed for these data, corresponding to long periods of exposure to environmental lead for most of the children. When individual data were not available, concentration ratios were calculated using mean concentration values for some parameters (cortical bone-to-blood, trabecular bone-to-blood, kidney-to-blood, liver-to-blood, and other soft tissues-to-blood).
- Compartmental concentration ratio estimates were converted into ratios of masses of lead using compartmental size (mass or volume). These ratios were then used to derive transfer times to and from model compartments.
- The relationship between blood and plasma was established, and the ratio of transfer times from red blood cells to plasma and from plasma to red blood cells was estimated.
- Once these parameters were fixed, the additional modifying terms of urinary, fecal, and other soft tissue elimination times were specified. Because of the long time needed to achieve steady-state in bone, (i.e., the long transfer time from bone to blood), the blood-to-bone transfer time was also designated.
- After a range of plausible parameter values was determined, model predictions using values within this range were compared to data from epidemiologic studies of blood lead in children from communities with measured environmental lead levels. These results were considered in the selection of specified parameter values within the varied ranges.

### Growth Equations

Many of the calculations in the biokinetic component require body fluid volumes and organ weights as a function of the age of the child. Growth equations (with the exception of bone) were fitted using a double logistic model (61,62), where the datasets for organ volume or weight were composites of childhood growth data from several handbooks (63,64). These equations follow the general formula for Equation 15, with the values for each tissue given in Table 3. Volumes are expressed in

**Table 3.** Biokinetic growth parameters for the general volume–weight equation (Equation 15) for each tissue.

	A	B	C	D	E	F
$Volume_{blood}(t)$	10.67	6.87	7.09	21.86	88.15	26.73
$Volume_{RBC}(t)$	4.31	6.45	10.0	26.47	129.61	25.98
$Volume_{plasma}(t)$	6.46	6.81	5.74	8.83	65.66	23.62
$Weight_{body}(t)$	8.375	3.80	3.60	17.261	48.76	20.63
$Weight_{kidney}(t)$	0.050	5.24	4.24	0.106	65.67	34.11
$Weight_{liver}(t)$	0.261	9.82	3.67	0.584	55.65	37.64

deciliters and weights in kilograms; age in months is  $t$ .

$$Volume(t) \text{ or } weight(t) = \left[ \frac{A}{1 + \exp\left(\frac{-(t-B)}{C}\right)} \right] + \left[ \frac{D}{1 + \exp\left(\frac{-(t-E)}{F}\right)} \right] \quad [15]$$

$$Weight_{bone}(t) = 0.111 \times Weight_{body}(t) \quad \text{for } t \leq 12 \text{ months} \\ = 0.838 + 0.02 \times t \quad \text{for } t > 12 \text{ months} \quad [16]$$

Bone weight is assumed to be a linear function of age for children older than 12 months, with slope and intercept parameters estimated by fitting a simple linear regression model to data from Harley and Kneip (49) (Equation 16). For younger children the weight of bone is assumed to be a constant percentage of body weight. Trabecular and cortical bone are assumed to account for 20 and 80%, respectively, of total bone weight (65). The weights of liver and kidney are estimated by Equation 15. For the other soft tissues compartment, the weight is obtained by subtracting the weight of all other body compartments from the weight of the body. The ECF volume is estimated as 73% of the blood volume for all ages. Blood is taken to have a density of 1.056 kg/liter.

### Tissue Lead Masses and Blood Lead Concentration at Birth

The process of determining lead masses in each of the body compartments and the blood lead concentration begins with the compartmental lead masses of a newborn child. The blood lead concentration of a newborn child is assumed to be 85% of the mother's blood lead concentration (default 2.5  $\mu\text{g}/\text{dl}$ ), based on data and relationships discussed in references (1,66,67). Bioconcentration ratios in newborn children, which were derived from data from Barry (18), were used with the estimated

newborn blood concentrations to calculate tissue lead burdens at birth. For newborn children the concentration ratios of cortical bone-to-blood, trabecular bone-to-blood, kidney-to-blood, liver-to-blood, and other soft tissues-to-blood are 7.9, 5.1, 1.1, 1.3, and 1.6  $\mu\text{g}/\text{kg}$  per  $\mu\text{g}/\text{liter}$ , respectively.

### Equations for Compartmental Lead Masses and Blood Lead Concentration

The differential equations that follow represent the continuous lead kinetics in a child's body (Equations 17–25). The variables beginning with  $M$  are the masses ( $\mu\text{g}$ ) of lead in the fluid and tissue compartments of the body. The masses of lead in the plasma–ECF, red blood cells, liver, kidney, other soft tissues, trabecular bone, and cortical bone compartments are designated as  $MPLECF$ ,  $MRBC$ ,  $MLIVER$ ,  $MKIDNEY$ ,  $MOTHER$ ,  $MTRAB$ , and  $MCORT$ , respectively. The variables beginning with  $T$  denote transfer times (days) between the compartments and to the elimination pools. See Table 4 for the definitions of these transfer times.

$$\frac{d}{dt} MLIVER = \frac{MPLECF}{TPLLIV} - \frac{MLIVER}{TLIVPL} - \frac{MLIVER}{TLIVFEC} \quad [17]$$

$$\frac{d}{dt} MKIDNEY = \frac{MPLECF}{TCLKID} - \frac{MKIDNEY}{TKIDPL} \quad [18]$$

$$\frac{d}{dt} MOTHER = \frac{MPLECF}{TPLOTH} - \frac{MOTHER}{TOTHP} - \frac{MOTHER}{TOTHOUT} \quad [19]$$

$$\frac{d}{dt} MTRAB = \frac{MPLECF}{TPLTRAB} - \frac{MTRAB}{TTRABPL} \quad [20]$$

$$\frac{d}{dt} MCORT = \frac{MPLECF}{TPLCORT} - \frac{MCORT}{TCORTPL} \quad [21]$$

$$\frac{d}{dt} MRBC = \frac{MPLECF}{TPLRBC} \left[ 1 - \frac{MRBC}{VOLRBC \times CONRBC} \right] - \frac{MRBC}{TRBCPL} \quad [22]$$

$VOLRBC$  is the volume of the red blood cells, and  $CONRBC$  is the maximum lead concentration capacity of the red blood cells (see below).

$$\frac{d}{dt} MPLECF = INFLOW - OUTFLOW + UPTAKE \quad [23]$$

$$OUTFLOW = -MPLECF \times KPLECF$$

Where,

$$KPLECF = \frac{1}{TPLLIV} + \frac{1}{TCLKID} + \frac{1}{TPLTRAB} + \frac{1}{TPLCORT} \\ = \frac{1}{TPLOTH} + \frac{1}{TPLUR} + \frac{1}{TPLRBC} \\ \times \left[ 1 - \frac{MRBC}{VOLRBC \times CONRBC} \right] \quad [24]$$

The term  $KPLECF$ , which is dimensionally a first-order rate constant ( $\text{day}^{-1}$ ), is in fact a variable because it involves the variable  $MRBC$ .  $KPLECF$  provides the instantaneous total rate of transfer out from the plasma–ECF.  $UPTAKE$  is equal to the sum of its active and passive components,  $UP_{active}$  (Equation 12) and  $UP_{passive}$  (Equation 14), respectively.

$$INFLOW = \frac{MRBC}{TRBCPL} + \frac{MLIVER}{TLIVPL} + \frac{MKIDNEY}{TKIDPL} + \frac{MOTHER}{TOTHP} + \frac{MTRAB}{TTRABPL} + \frac{MCORT}{TCORTPL} \quad [25]$$

**Table 4.** Biokinetic transfer times for the IEUBK model.

Variable name <sup>a</sup>		Value at age 2 years, days
Intercompartment transfer times		
Blood to bone		1
Blood to kidney		10
Blood to liver		10
Blood to other soft tissues		10
Bone to blood		12.3
Cortical bone to plasma	TCORTPL	12.3
Trabecular bone to plasma	TTRABPL	12.3
Kidney to plasma	TKIDPL	1.5
Liver to plasma	TLIVPL	38.4
Other soft tissue to plasma	TOTHPL	656
Red blood cells to plasma	TRBCPL	10.0
Plasma to cortical bone	TPLCORT	0.012
Plasma to trabecular bone	TPLTRAB	0.05
Plasma to kidney	TPLKID	0.1
Plasma to liver	TPLLIV	0.1
Plasma to other soft tissues	TPLOTH	0.1
Plasma to red blood cell	TPLRBC	0.1
Elimination times		
Blood to urine		20.0
Plasma to urine	TPLUR	0.2
Blood to feces		15.0
Liver to feces	TLIVFEC	19.2
Blood to soft tissue elimination pool		11.2
Soft tissue to elimination pool	TOTHOUT	82.0

<sup>a</sup>For variables used in equations in this article; other variables used in intermediary calculations per text.

Blood lead concentration is calculated from the lead masses in the compartment volumes of plasma and red blood cells.

The computer model uses analogous nonlinear difference equations with discrete time steps in its computations in place of the differential equations that describe continuous lead kinetics. The difference equations represent lead masses, transfer rates, and elimination rates at the beginning and end of a time interval.

### Compartmental Transfer Times

The compartmental lead transfer times account for the movement of lead between the plasma–ECF compartment, the tissue compartments (red blood cells, liver, kidney, trabecular and cortical bone, and other soft tissues), and the elimination pathways. The model determines the compartmental lead transfer times as a function of tissue to blood lead concentration ratios and the ratio of lead masses in blood to plasma–ECF. Transfer times are expressed on a plasma basis. At steady state, the ratio of the mass of lead in any of the tissue compartments to the mass of lead in the plasma–ECF compartment equals the ratio of the transfer time from tissue to the plasma–ECF compartment to the transfer time from the plasma–ECF compartment to tissue. Because data were not available to allow separate estimates of transfer times

into and out of most compartments, the ratio of transfer times was determined.

Transfer times from red blood cells to plasma and from plasma to red blood cells were estimated from adult data (50,61–64, 66,68–72). Except for the plasma–ECF compartment to red blood cell transfer that assumes saturable lead holding capacity of the red blood cells, the model assumes that lead is transported between the central plasma–ECF compartment and other compartments by a first-order kinetic process with rate coefficients that are independent of compartmental lead concentrations. Nonlinearity occurs when red blood cells are saturated at a maximum lead holding capacity (*CONRBC*) of 1200 µg/dl, based on estimates for adults (73) and infant baboons using data in Mallon (24) as reanalyzed by Marcus (74). This value is consistent with studies that show a roughly constant ratio of plasma lead concentration to blood lead concentration when blood lead concentrations are less than 40 to 60 µg/dl, with nonlinearity at higher concentrations

(68,69) as reanalyzed in Marcus (52). To maintain mass balance in near steady-state conditions, the relationship between plasma and red blood cells was obtained by fixing the ratio of masses to correspond to the tissue/blood lead concentration ratios of Barry (18), the ratio of blood/plasma, and the weight of the red blood cell tissues and volume of the plasma–ECF pool.

**Allometric Scaling.** Coefficients were estimated for lead transfer times from blood to urine, liver, kidney, bone, and other soft tissues. The transfer times between compartments take the general form of the product of the concentration ratio, the weight or volume ratio, and the transfer coefficient (exemplified by Equation 26). The factor of 10 in Equation 26 accounts for the blood volume being expressed in deciliters. The concentration ratio has the general form of Equation 27, with the parameter values in Table 5. The transfer times (Table 4) were scaled allometrically by the ratio of body weight to the weight of a child at 24 months of age (12.3 kg) raised to the 1/3 power. The 1/3 power scaling exponent for transfer times (or –1/3 power for transfer rates) corresponds to surface area scaling for growing children. In other words, the increase in organ surface area is proportional to the 2/3 power of the child's weight increase, and the increase in weight is a function of the child's age. Although the empirical value of 0.26 fits better than 0.33 for some applications (75), the difference is numerically unimportant in this age range where the child grows only from 3.4 to 20 kg.

$$\text{Transfer}_{\text{kidney-plasma}}(t) = \text{ConcRatio}_{\text{kidney-blood}} \times \frac{\text{Weight}_{\text{kidney}}(t)}{\text{Volume}_{\text{blood}}(t)/10} \times \text{Transfer}_{\text{blood-kidney}}(t) \quad [26]$$

$$\text{ConcRatio}(t) = A + B \times (1 - \exp(C \times t)) \quad [27]$$

Where *A*, *B*, and *C* are constants and *t* is age.

**Table 5.** Concentration ratio parameter values (µg/kg Pb tissue per µg/liter Pb blood).

	A	B	C
<i>ConcRatio</i> <sub>kidney-blood</sub>	0.777	2.35	–0.0468
<i>ConcRatio</i> <sub>liver-blood</sub>	1.1	3.5	–0.0462
<i>ConcRatio</i> <sub>bone blood</sub>	6.0	215	–0.000942
<i>ConcRatio</i> <sub>other tissue-blood</sub>	0.931	0.437	–0.00749

**Determination and Calibration of Transfer Coefficients.** The ratio of lead mass in blood to lead mass in plasma-ECF was set at a constant 100 to reflect low lead concentrations when the red blood cell is nearly unsaturated. A nominal transfer time of 0.1 was assigned directly to the plasma-ECF compartment to red blood cell lead. The calculated blood lead concentration shows little dependence on the lead transfer time from plasma-ECF compartment to red blood cells for a wide range of values once blood lead to plasma lead ratio is specified.

Fixing the value of the blood lead to plasma ratio also affects other parameters, including the red blood cell to plasma-ECF compartment transfer time and the relationships of transfer times from blood to urine, plasma to urine, blood to bone, and plasma to bone. The lead transfer times from plasma to tissues (liver, kidney and other soft tissues) are also related to the ratio of blood lead to plasma lead.

In the IEUBK model, a simplified approximation of bone lead kinetics was used to model the relationship between bone and blood in young children. The model was designed for applications where there are long periods of relatively steady exposure, not to acute or relatively rapid subchronic exposures, so that only the slowest transfer components affect kinetics on the time scales of interest. The cortical and trabecular compartments in the model provide the potential for long-term retention and storage of lead as an endogenous source.

The lead transfer times from the trabecular bone and cortical bone to the plasma-ECF compartment are assigned a similar transfer coefficient. The transfer times from the plasma-ECF compartment to the bone compartments (trabecular and cortical) are calculated as the ratio of the transfer time from blood to bone to a percentage of the ratio of lead mass in blood to lead mass in plasma-ECF (20% of this ratio for the trabecular bone and 80% for cortical bone).

**Elimination Rates.** The elimination times are shown in Table 4. The transfer coefficient for blood to urine, which was estimated by the process described above, is the blood lead mass divided by the rate at which lead is eliminated from the blood through the urine. A literature review revealed seventeen adult studies for evaluating this coefficient (46,51,76-90). The adult value was allometrically scaled to children 0 to 84 months of age, based on proportionality between the blood volume

and glomerular filtration rate for that age group. Because the glomerular filtration rate is proportional to body surface area for infants and toddlers (91) and for children older than 24 months (92), scaling by surface area is equivalent to scaling by glomerular filtration rate.

The lead transfer time from blood through the bile duct to feces was calculated as the product of the transfer time from blood to urine and the ratio of endogenous fecal lead transfer time to urinary transfer time. The ratio of elimination times of 0.75 was estimated for adults using data from Chamberlain et al. (46,93) and is assumed to apply to ages 0 to 84 months. In the model, the endogenous fecal elimination is treated mathematically as a direct elimination from the liver. A steady-state mass balance calculation is used to determine the elimination time constant from the liver via the feces in terms of the transfer time from the blood to endogenous fecal excretion. The lead transfer time from blood to the elimination pool via the soft tissue is the product of the lead transfer time from blood to feces and the ratio of the elimination time via soft tissues to the endogenous fecal elimination time set at 0.75. The elimination time from the other soft tissue pool is then determined from the elimination time from the blood to this pool using a mass balance calculation at steady state.

Mass balance between uptake and elimination was achieved by assigning values for excretion that were within plausible ranges. Because of the lack of data for elimination rates in children, there was considerable uncertainty in the values for excretory parameters. To maintain mass balance, the elimination parameters were set at the high end of the plausible range; this will tend to yield lower estimates of blood lead levels than would more central estimates for these parameters. If future research supports significant changes to influential model parameters affecting estimated exposure levels from lead soil and dust (bioavailability, soil ingestion, etc.), a recalibration of the model would be indicated.

Lead concentrations in each biokinetic compartment are calculated from infancy to 84 months of age. The exposure parameters for the model are intended to represent reasonable central estimates for the amount of lead ingested or inhaled per unit time. The model calibration step described above made adjustments to a few biokinetic parameters to improve the agreement between the point estimates of blood levels

from the biokinetic component, and measured geometric mean values for blood lead levels seen in studies where both exposure information and blood lead data were available for populations of children. Accordingly, the point estimate of blood lead obtained from the biokinetic compartment of the model is treated as a geometric mean estimate about which the blood lead distribution is centered.

## Variability

An important goal of the IEUBK model is to address the variability in blood lead levels among exposed children. Children having contact with the same concentrations of environmental lead can develop very different blood lead levels due to differences in behavior, household characteristics, and individual patterns of lead uptake and biokinetics. The variability or stochastic component of the IEUBK model uses a lognormal probability model for blood lead concentrations to address these expected differences. The log-normal model is specified in a two step process. First, in developing the exposure, uptake, and biokinetic calculations, a general goal was to use values that were central or typical for exposure factors and pharmacokinetic parameters. Using these inputs, the compartmental model generates a central tendency estimate of blood lead concentration specific to the combination of environmental lead concentrations being assessed. This central tendency estimate provides the GM blood lead level for the log-normal model. Second, an empirically based geometric standard deviation (GSD) represents the expected variability in blood lead levels among children exposed to the specified concentrations of environmental lead. The log-normal model provides an estimate of the probability that individuals will have blood lead concentrations exceeding a level of concern.

The GSD parameter for the log-normal model is an empirical estimate, derived from epidemiologic studies, of the amount of variability in blood lead levels seen in children exposed to similar concentrations of environmental lead. Different children exposed to the same residential lead concentrations will have different blood lead levels because of a diverse set of factors:

- Differences in the outdoor residential environment, e.g., the nature of play surfaces (sod, amount of exposed soil, paving)
- Differences in the indoor home environment, e.g., carpeting, smooth bare surfaces, poorly cleanable surfaces

- Housekeeping differences, e.g., cleaning and maintenance patterns affecting the amount and accessibility of indoor dust
- Differences in children's behavior and play activities, e.g., mouthing of hands, toys and surfaces
- Differences in children's eating habits that affect soil and dust exposures, e.g., taking food outdoors
- Biologic diversity affecting the absorption, distribution, and elimination of lead in children
- Variability of lead concentrations within residential properties leading to exposures that vary depending on activity locations (not all children will be exposed to the lot average concentrations)

These factors reflect variability at the individual or household level as opposed to variability within a community. In a community, concentrations of lead in household soils and dusts will often vary substantially between different residences. The individual level GSD used in the IEUBK model does not account for diversity of exposures to the varying concentrations of environmental lead within a community.

### Estimating a Geometric Standard Deviation

The recommended default GSD for the IEUBK model is 1.6, which is intended as a broadly applicable, not a conservative, value. Data from several epidemiologic studies with paired environmental and blood lead measurements were examined in the development of the recommended GSD value, and alternate statistical approaches were evaluated. As an example, blood lead and residential environmental lead measurements were available from a 1989 study of a population of children in Midvale, Utah, a community where smelting operations had been conducted (94). Several approaches to estimating a GSD were applied with this dataset (10). First, a stratification approach was applied in which children participating in the study were subdivided into cells according to age and measured soil and dust lead concentrations. Within-cell GSD terms were then calculated to represent the variability in blood lead levels among children of a similar age exposed to similar concentrations of environmental lead. The median of the within-cell GSD values was approximately 1.7; when weighted by the degrees of freedom, the median was 1.8. The standard statistical approach of calculating a pooled within-cell variance (on a log scale) yielded a GSD estimate of approximately 1.9. As an alternative approach, a nonlinear regression

relating blood lead to age and soil and dust lead concentrations was fit to the Midvale data. The residual variance from the regression fit provided a GSD estimate of 1.8 (95% confidence interval 1.6–1.9).

GSD estimates, using the stratification methodology, were developed for two other community studies, the Baltimore, Maryland, data from the Urban Soil Lead Abatement Demonstration Project (95) and an environmental health study in Butte, Montana (96). Weighted median GSD's of approximately 1.5 and 1.6 were obtained, respectively, for the Baltimore and Butte datasets. Marcus (97) has also reported GSD estimates for several mining and smelter sites ranging from 1.30 to 1.79.

Consideration must be given to the interpretation of these results. Environmental lead measurements are not fully reproducible because of sampling location variability, repeat sampling variability, and analytical error. Data points that appear to be unusually high or low (potential outliers) are also encountered, at times, in blood lead studies. The median GSD calculation is likely to be relatively robust to the presence of potential outliers and measurement error in the study data sets. For these reasons, median calculations were emphasized in selecting default parameter estimates for the IEUBK models.

Nevertheless, median estimates of the GSD have a statistical tendency to underestimate the true GSD. To evaluate the importance of this tendency, we conducted a statistical simulation using random log-normal variables with a GSD of 1.8. The simulation, using the same numbers of observations per cell as in the Midvale study, found that median-based GSD estimates were lower than the correct value of 1.8. GSD estimates of 1.66 and 1.60 were obtained for the weighted median and unweighted median calculations, respectively. A standard pooled variance estimate closely reproduced the correct GSD (calculated GSD 1.81), as would be predicted by statistical theory.

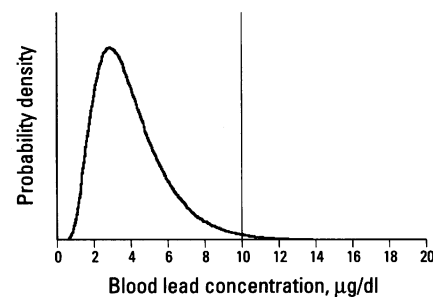
The alternate approach discussed above obtained a GSD estimate from the residuals in a nonlinear regression calculation. In this type of approach, it is important that the regression equations and the IEUBK model provide a comparable level of specification of a child's environment. Specifically, the IEUBK model has variables representing soil and dust lead concentrations but not variables representing demographics, household cleanliness (e.g., dust loadings), or children's behavior (e.g., mouthing tendencies).

Although the latter variables may be important to obtaining an optimal fit in regression modeling, GSD estimates obtained from such models may be expected to be lower than would be appropriate for the IEUBK model.

### Model Output

For risk assessment purposes, the primary application of the IEUBK model is to project individual risks of elevated blood lead. In the simplest situation, the model uses measurement data on the environmental lead concentrations for a residence to project a plausible distribution of blood lead levels for any children who might live there (either currently, or in the future, due to turnover of residents). The probability of exceeding a blood lead level of concern, currently 10 µg/dl, is calculated using a log-normal probability model as described above. The output from the IEUBK computer program provides estimated probabilities of elevated blood lead levels along with graphical displays of the modeled blood lead probability distribution. Figure 5 provides an example of a modeled probability density function for blood lead concentrations. This distribution was obtained using model default values for all parameters, including the (illustrative) concentration values of 200 ppm of lead in soil and dust. Under these conditions the model predicts a relatively small probability (0.015 or 1.5%) that an exposed child would have a blood lead level in excess of 10 µg/dl.

The IEUBK model can also be used to calculate risk-based goals for environmental remediation. This application is a direct extension of the approach to estimating individual risks of elevated blood lead concentrations. The model user must specify a target blood lead level for health protection and a target probability to limit the risk of



**Figure 5.** Example probability density function output by the IEUBK computer model. Default values were used for all model parameters including 200 ppm soil lead and 200 ppm dust lead. GM=3.6, GSD=1.6, probability > 10 µg/dl = 0.015.

exceeding this level. U.S. EPA guidance under the Superfund Program identifies a goal that a child would have of no more than a 5% risk of exceeding a blood lead concentration of 10 µg/dl (98). A sequence of model calculations can then be performed to identify the environmental concentrations at which the target risk level would be exceeded. The IEUBK computer program provides tools to simplify the process of performing such a sequence of runs. The model user must ensure that an appropriate set of modeling assumptions is maintained in this process. For example, if a risk-based goal for soil contamination is being determined, the user will normally link indoor dust lead levels to the soil lead levels.

At times it is useful to estimate the overall risk of elevated blood lead for a population or group of children. (However, it is important to note that population risk calculations can mask the occurrence of high levels of individual risk, by averaging high risk individuals in with a larger group in which many individuals may be at low risk.) In population-based analyses, a representative set of residence-specific environmental lead levels must be input, in sequence, to the IEUBK model. The estimated fraction of the population with elevated blood lead levels is then obtained by summing the calculated individual risks of elevated blood lead associated with each combination of environmental lead. Note that since communities can be expected to differ from each other in the relative extent and combinations of multimedia lead contamination, the IEUBK model was purposely not designed to generate blood lead distributions from community mean environmental lead levels. That is, a single run of the program using community or neighborhood wide means for soil and dust lead concentrations cannot be relied upon to generate a blood lead distribution that describes the resident population. Risks calculated using area-wide mean environmental lead levels will only be applicable to those children whose own exposures happen to match the mean levels.

Model applications can also facilitate the consideration of alternate exposure scenarios, for example, by examining the impact of lowering the lead concentration in a particular environmental medium. Comparisons of the risks attributable to particular exposure pathways can provide support for decisions about environmental remediation options.

Some caveats must be stressed concerning constructive use of the IEUBK model. As with any model, the inputs must be

relevant for the application and users must develop relevant site-specific exposure scenarios. Also, while the IEUBK program provides estimates of GM blood lead levels on a residence-by-residence basis, users are reminded that these predicted means are, by definition, "most likely" values. Blood lead levels in resident children are not expected to match the predicted GM values but, rather, are predicted to fall in a relatively broad range around the GM values.

The analysis of the concordance between model predictions and data sets with blood lead levels and concurrently measured environmental lead levels is best carried out with a thorough understanding of the specific attributes and methods of each sampling protocol. An accompanying paper details an evaluation of the concordance between observed and predicted blood lead levels for three epidemiologic datasets (4). Briefly, residence-specific environmental lead measurements from the three datasets were used as inputs for the IEUBK model and model predictions of blood lead levels were compared with the measured blood lead levels for children living in those residences. Comparisons, developed for children who did not spend extended periods at daycare or other unsampled locations, showed a reasonably close agreement between the observed and predicted blood lead distributions in the three studies. The observed and predicted GM blood lead levels were within 0.7 µg/dl, and the proportions of the study populations estimated to be above 10 µg/dl were within 4% of those observed.

## Discussion

The goal of the IEUBK model is to provide appropriate, unbiased, estimates of the blood lead concentrations that can be expected to occur in children who have contact with environmental lead. The model predictions are intended to be unbiased in the sense that model parameters were selected with the goal being reasonable best estimates, rather than with the intent of building conservatism into the model predictions. There are significant parameter uncertainties inherent in a complex model of this nature. As a step to control the impact of these uncertainties, the developers of the IEUBK model took advantage of the opportunity to calibrate model predictions with reference to the results of two significant field studies in the United States, in which data on both environmental and children's blood lead levels were collected. The goal of the model calibration exercise, which involved fine

tuning selected biokinetic equations, was to refine the ability of the model to provide reasonable, unbiased estimates of blood lead levels in children.

The approach of the IEUBK model in predicting children's blood lead levels can be compared with other potential approaches for assessing risks from lead. In regression or "slope factor" approaches to evaluating lead risks, statistical models are fit to datasets with paired measurements of environmental and blood lead. Although regression models and resulting slope factor estimates have contributed to our understanding of environmental lead risks, two important qualifications need to be considered. First, the statistical forms of regression models that are convenient and statistically consistent with the skewed probability distributions seen with environmental lead data can lead to biologically implausible relationships. For example, a multiple linear regression model may be fit to relate log scale values of environmental measurements to the log scale blood lead concentrations. However, this mathematical form implies that the effect of lead in any one environmental medium on blood lead depends multiplicatively, rather than additively, on the lead levels observed in all other environmental media that are assessed. Also, under a log scale model, the shape of the predicted relationship between environmental and blood lead levels can lack plausibility. Blood levels may be predicted to increase sharply at low levels of environmental lead, followed by a flat, insensitive relationship at higher environmental levels where greater health concerns would be anticipated.

It should also be noted that when significant measurement error is present in the independent variables (here, the environmental lead levels), results from uncorrected regression models will be biased to underestimate the strength of the true relationship between environmental lead and blood lead. Appropriate statistical tools are available to reflect the plausible shape of the environmental lead/blood lead relationship and, with some limitations, to address the effects of measurement errors on parameter estimates (99). However, it is worth emphasizing that statistical modeling for blood lead relationships involves complicated issues of model form and interpretation. As with other complex models, considerable care needs to be given to the formulation and validation of statistical models, and such models should not be uncritically assumed to provide a straightforward representation of empirical truth.

Another assessment tool that is currently receiving considerable attention for environmental applications is Monte Carlo simulation. Conceptually, a Monte Carlo-based approach to assessing environmental lead risks could be constructed that would have much in common with the IEUBK model. If data on statistical distributions for important model parameters were developed, and if data were available to address correlations or statistical dependence among model parameters, a Monte Carlo simulation could be developed to arrive at estimates of the distribution of children's blood lead levels. Such a model would use the propagated variability from the distributions for model input parameters to assess the variability in blood lead levels (in contrast to the IEUBK model's application of an empirically based GSD). Although the Monte Carlo paradigm has considerable conceptual appeal, the authors' experience in reviewing the available database during the development of the IEUBK model indicates that distributional estimates for many significant exposure and biokinetic parameters would necessarily be highly speculative and heavily based on personal judgment. Additionally, data on potential correlations among model input parameters is largely absent. Under these circumstances, we think there are distinct advantages in relying on data on children's blood lead levels from environmental epidemiologic investigations to develop an empirical GSD estimate (that by construction encompasses variability among children in aspects of all model compartments—exposure, uptake, and biokinetics).

It is worthwhile to compare the application of the IEUBK model as a tool to support environmental decision making to the approach using reference doses (RfDs) that the U.S. EPA generally uses to assess non-carcinogenic risks from chemical contaminants. Current U.S. EPA risk management guidance for lead is focused on limiting exposures such that children exposed to environmental lead would not have a risk of greater than 5% of exceeding a blood lead level of 10 µg/dl (98). There is agreement among the U.S. federal agencies that the avoidance of blood lead levels above 10 µg/dl in sensitive population groups (including children) is an important goal for health protection (6–8). The level of 10 µg/dl may be considered to be a low effect level in that epidemiologic literature relates observed decrements in mental performance in children to blood lead levels of 10 µg/dl or lower (6). In contrast, U.S. EPA interprets RfD values for other compounds as levels at

or below which adverse health effects are unlikely to occur. If an RfD approach using uncertainty factors were applied to lead, the predicted safe levels would probably be placed significantly below 10 µg/dl.

During the development of the IEUBK model, U.S. EPA researchers have tried to make optimal use of the diverse available data on lead exposures of children and lead pharmacokinetics. However, further research can strengthen the database for estimation of some important model parameters. Several examples can be given in which further research could support refined estimates of model parameters.

Data to distinguish children's lead exposures from indoor dust versus outdoor soil are sparse. In other assessment contexts, where indoor sources of contaminants have not been a key issue, assessors have avoided this problem through the use of exposure estimates based on total soil ingestion (reflecting intake of both outdoor soil and the soil-derived fraction of indoor dust). However, indoor sources of lead in dust (e.g., from lead-based paint) can be important to children's overall lead exposures, thus necessitating an approach that disaggregates soil and dust exposures. Further research relating to factors influencing the transport of soil into house dust and addressing the relative rates of dust ingestion in the indoor and outdoor environments could strengthen lead risk assessments.

Relatively little information is available addressing how exposure, uptake, or biokinetic parameters change across the age range that is assessed in the IEUBK model (0–84 months). Where appropriate, the model uses allometric scaling to address age-related changes in biokinetic parameters. More age-specific data would be valuable. For example, data to address the age dependence (within childhood) of the bioavailability of ingested environmental lead is very sparse. The IEUBK model is currently implemented using constant values for the low dose absorption fractions of lead from environmental media; allometric scaling is used to address the plausible effect of growth on the saturation parameter for absorption from the gut. Under these assumptions older children can be estimated to have somewhat higher absorption fractions than younger children (less saturation of uptake is assumed for older children and thus the net absorption is closer to that indicated by the low dose absorption fraction). Further research on the age dependence of lead absorption in children could strengthen model estimates of age-specific patterns in

blood lead. Finally, the excretion parameters in the biokinetic component of the model are specified at relatively high values. Lower values would be also plausible and would lead to the prediction of higher blood lead levels. Only limited data are available for excretion rates for urinary, fecal, and other pathways of lead elimination in children. Field or clinical investigations, addressing children with a history of exposure to lead, could support more direct estimates of excretion parameters.

In the U.S. EPA's experience, the IEUBK model is proving to be a valuable tool in meeting the agency's goals of addressing multimedia exposures, examining interindividual variability, and applying methods that support greater realism in risk assessment. In comparison with many tools used in environmental assessment, the predictions of the IEUBK model are well grounded and supported by comparisons with empirical data sets. However, as further data are developed on the details of environmental lead exposures and the processing of lead in the human body, the framework established in the IEUBK model will support refined estimates of the risks from environmental lead.

## Appendix

### Software and Documentation for the IEUBK Model

Information about the IEUBK model and technical support available through the U.S. EPA Technical Review Workgroup for Lead is accessible on the Internet: [www.epa.gov/superfund/programs/lead/index.htm](http://www.epa.gov/superfund/programs/lead/index.htm)

The following IEUBK model computer program and two primary supporting references are available for purchase through the National Technical Information Service (NTIS, Technology Administration, Springfield, VA 22161. Telephone: (703) 605-6000. Fax: (703) 605-6900):

- Integrated Exposure Uptake Biokinetic Model for Lead in Children (IEUBK). Version 0.99D/ NTIS No. PB94-501517/ Publ No. 9285.7-15-2.
- Guidance Manual for the Integrated Exposure Uptake Biokinetic Model for Lead in Children (February 1994). NTIS No. PB93-963510. Publ No. 9285.7-15-1.
- Technical Support Document for the Integrated Exposure Uptake Biokinetic Model for Lead in Children (December 1994). NTIS No. PB94-963505. Publ No. 9285.7-22.



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